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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,782	05/10/2002	Johan Memelink	BO 43339	7997
466	7590	01/12/2006	EXAMINER	
YOUNG & THOMPSON 745 SOUTH 23RD STREET 2ND FLOOR ARLINGTON, VA 22202			COLLINS, CYNTHIA E	
			ART UNIT	PAPER NUMBER
			1638	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/890,782	Applicant(s) MEMELINK ET AL.	
	Examiner Cynthia Collins	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on October 26, 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 49-73 is/are pending in the application.
- 4a) Of the above claim(s) 57-65 and 69-72 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 49-56, 66, 68 and 73 is/are rejected.
- 7) ☒ Claim(s) 67 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input checked="" type="checkbox"/> Other: <u>attachments 1 and 2</u> . |

DETAILED ACTION

The Amendment filed October 26, 2005 has been entered.

Applicant notes that while the Official Action indicated that claims 25-48 are pending in the present application, the preliminary amendment filed with the present application canceled claims 1-28 and added new claims 29-52. Therefore, applicants believe that the new claims should start at claim 53. (reply page 10)

As noted at page 2 of the office action mailed October 21, 2004, claims 29-52 were renumbered as claims 25-48 in accordance with rule 1.126, because no claims numbered 25-28 were pending upon entry of the preliminary amendment filed August 6, 2001. See also the copy of claims pending upon entry of the preliminary amendment filed August 6, 2001 and fee worksheet, attached. Accordingly, newly submitted claims 53-77 are renumbered as claims 49-73 in accordance with rule 1.126.

Claims 1-48 are cancelled.

Claims 49-73 are newly added.

Claims 49-73 are pending.

Newly submitted claims 57-65 and 69-72 correspond to subject matter previously withdrawn from consideration at page 3 of the office action mailed April 26, 2005 (claims 37-47). Accordingly, claims 57-65 and 69-72 are also withdrawn from consideration. Claims 49-56, 66-68 and 73 are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

Claims 49-56, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the office action mailed April 26, 2005.

Applicants' arguments filed October 26, 2005 have been fully considered but they are not persuasive.

Upon reviewing new claims 53-77, applicants believe that the present disclosure describes a representative number of species falling within the scope of the claimed invention. In particular, the Examiner's attention is respectfully directed to independent claim 53, which recites a method of modulating in the plant cell the levels of one or more terpenoid indole alkaloids (TIAs), and/or of modulating the expression of one or more genes responsible for the biosynthesis of a TIA or a precursor thereof. The method itself recites a step of providing to the cell an AP2-domain transcription factor that is jasmonate responsive and comprises at least one Ap2-domain having an amino acid sequence with at least 80% amino acid identify with SEQ ID NO:6. Dependent claims further characterize the TIAS (claim 58) and the species of the plant cell (claims 63-65). The AP2-domain comprises SEQ ID NO:6 (claims 72-76). As to new claim 77, claim 77 is dependent on claim 53 and further characterizes the genetic construct, the Ap2-domain itself, the species of the plant cell, and the type of TIA. Support for these claims can be found throughout the description and in particular on page 2, line 23 for the recited TIAS and on page 8, lines 20-25 for the recitations directed to the recited Ap2-domain transcription factor and

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nucleotide sequences. Support for the recitations directed to the plant species may be found in the present specification at page 38, lines 1-10. (reply pages 10-11)

Applicants' arguments are unconvincing. The Examiner maintains that the two nucleotide sequences described (SEQ ID NOS: 2 and 3) which were obtained from a single plant species (*Catharanthus roseus*), which encode AP2-domain transcription factors that comprise a single Ap2 domain, and which are natively expressed in response to jasmonate treatment of *Catharanthus roseus* cells, are not representative of the claimed genus which encompasses numerous undisclosed and uncharacterized sequences obtained from any source that encode AP2-domain transcription factor variants that comprise one or more Ap2 domains having an amino acid sequence with at least 80% amino acid identity with SEQ ID NO:6 and that are responsive in any way to jasmonate.

Claims 49-56, 66, 68 and 73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleotide sequence encoding SEQ ID NO:6, for nucleotide sequences encoding the truncations of SEQ ID NO:6 that are disclosed as $\Delta 5ORCA3$ and $\Delta 3ORCA3$, and for methods of transforming *Catharanthus roseus* cells with said nucleotide sequences operably linked to a promoter in a sense orientation, does not reasonably provide enablement for nucleotide sequences encoding variants of SEQ ID NO:6, or for other methods of using nucleotide sequences encoding SEQ ID NO:6 or truncations or variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record set forth in the office action mailed April 26, 2005.

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Applicant's arguments filed October 26, 2005 have been fully considered but they are not persuasive.

Applicants believe the present amendment obviates this rejection. Applicants point out that it is a well founded principle that any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. Applicants maintain that, as matter law, the expressed teaching of the patent specification cannot be controverted by mere speculation and unsupported assertions on the part of the Patent Office. As noted above, claims 29-52 have been canceled. As to new claims, applicants believe that the rejection fails to satisfy its burden in showing that the present application is not enabling the scope of the current claims. Indeed, Applicants point out that the claims have been amended to recite TIAS instead of any and types of metabolites. Furthermore, the claims further characterize the Ap2-domain transcription factor and recite nucleotide sequences. Claims have also been added to select a number of enzymes that are shown to be under control of the Ap2-domain transcription factor as set forth in the present specification page 29, lines 10-15. Claims 64-65 and 77 further characterize the taxonomic classification of the plant cell. Thus, claims 64-65 and 77 are not directed to any and types of plants. Rather, claims 64-65 and recite the family, order, genus, and/or species of the recited plant/plant cell the claims. As a result, applicants believe that the Office Action fails to satisfy its burden in showing that the recited embodiments directed to the type of TIA, plant transcription factor and nucleotide sequence are not enabled by the present disclosure. (reply pages 11-13)

Applicants' arguments are unconvincing. The evidence and reasoning substantiating the basis for the rejection is set forth in detail at pages 9-17 of the Office Action mailed April 26, 2005.

The Examiner also maintains that the amendment of the claims to recite TIAs instead of any and types of metabolites does not enable the full scope of the claimed invention because the outstanding rejection was not solely predicated on the type of metabolite modulated, and because the effect of expressing SEQ ID NO:6 or variants thereof on the level of TIAs such as serpentine, ajmalicine, vincristine, vinblastine, camptothecine, quinine, quinidine, reserpine, strictosidine, rescinnamine, ellipticine and precursors and/or intermediates therefore is unpredictable, as the induction of a subset of genes encoding some of the enzymes required for TIA biosynthesis may not result in an increase in the level of any particular TIA.

See, for example, Memelink J. et al. (ORCAization of jasmonate-responsive gene expression in alkaloid metabolism. Trends Plant Sci. 2001 May;6(5):212-9. Review), who teach that while overexpression of ORCA3 (the AP2-domain transcription factor of SEQ ID NO:6) in *Catharanthus roseus* cells increases the expression of the TIA biosynthetic genes *Tdc*, *Str*, *Cpr* and *D4H*, overexpression of ORCA3 in these same cells does not result in a detectable increase of TIAs in these cells, possibly because the terpenoid branch of the TIA biosynthetic pathway is limiting for TIA production (page 216 column 2).

In the instant case the specification does not provide sufficient guidance with respect to how to use SEQ ID NO:6 or variants thereof to modulate the level of TIAs such as serpentine, ajmalicine, vincristine, vinblastine, camptothecine, quinine, quinidine, reserpine, strictosidine, rescinnamine, ellipticine and precursors and/or intermediates therefore. Absent such guidance

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one skilled in the art would have to alter or modify the conditions under which SEQ ID NO:6 or variants thereof are expressed in cells in order to determine the specific conditions under which the level of TIAs such as serpentine, ajmalicine, vincristine, vinblastine, camptothecine, quinine, quinidine, reserpine, strictosidine, rescinnamine, ellipticine and precursors and/or intermediates therefore could be modulated. Such a trial and error to practicing the claimed invention would constitute undue experimentation.

The Examiner additionally maintains that the amendment of the claims to recite that the Ap2-domain transcription factor is “jasmonate responsive” and comprises at least one AP2-domain having an amino acid sequence with at least 80% amino acid identity with SEQ ID NO:6 does not enable the full scope of the claimed invention because the outstanding rejection was not solely predicated on the type of Ap2-domain transcription factor used, and because the effect of expressing nucleotide sequences encoding variants of the Ap2-domain transcription factor that comprise at least one Ap2-domain having an amino acid sequence with at least 80% homology to AP2-domain of SEQ ID NO:6 is unpredictable, as the functional effect of altering the amino acid sequence of an Ap2-domain transcription factor or altering the number Ap2-domains in an Ap2-domain transcription factor is unpredictable. Further, the limitation “jasmonate responsive” is indefinite with respect to the Ap2-domain transcription factor.

The Examiner further maintains that the addition of claims directed to a select a number of enzymes that are shown to be under control of the Ap2-domain transcription factor does not enable the full scope of the claimed invention because the outstanding rejection was not solely predicated on which enzymes are under control of the Ap2-domain transcription factor, because the effect of expressing SEQ ID NO:6 or variants thereof on the expression of genes other than

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Tdc, *Str*, *Cpr*, *D4h*, *Asa* and *Dxs* is unpredictable, as SEQ ID NO:6 and variants thereof would require the presence of particular cis-acting sequences in the promoters of metabolite biosynthetic genes in order to mediate their effects, and not all metabolite biosynthetic genes would comprise the requisite cis-acting sequences in their promoters, and because not all of the rejected claims are limited to a select a number of enzymes that are shown to be under control of the Ap2-domain transcription factor.

The Examiner also maintains that the addition of claims directed to the taxonomic classification of the plant cells does not enable the full scope of the claimed invention because the outstanding rejection was not solely predicated on the type of cell used, because the desired results cannot predictably be achieved using cells other than *Catharanthus roseus* cells, as other types of cells may or may not comprise the appropriate native genes having requisite cis-acting sequences for SEQ ID NO:6 in their promoters, and because not all of the rejected claims are limited to the use of a particular type of cell.

Claims 49 and 66, and claims dependent thereon, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 49 and 66 are indefinite in the recitation of "an AP2-domain transcription factor that is jasmonate responsive". It is unclear in what way the AP2-domain transcription factor is responsive to jasmonate, as a protein may respond to a chemical in more than one way, and the nature of the response cannot be discerned from the elements recited in the claim.

Allowable Subject Matter

Claim 67 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins
Primary Examiner
Art Unit 1638

CC



12/29/05